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Factors affecting the approaches and complications of surgery in childhood papillary thyroid carcinomas

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ABSTRACT

Background: The aim of the study is to analyse the factors related to permanent surgical complications in children and adolescents with papillary thyroid carcinoma treated by total thyroidectomy with central and bilateral neck dissections.

Methods: Children and adolescents aged ≤18-year-old at presentation with papillary thyroid carcinoma during the years 1988–2010 underwent thyroid and lymph-node surgeries (with a median follow-up of 19.6 years) were analysed for post-surgical complications.

Results: Permanent surgical morbidity occurred in 14% (n = 70) of patients who underwent total thyroidectomy as well as bilateral central and lateral neck dissections (n = 509). Factors associated with permanent complications included pN1 with extra-nodal extension, > 4 metastatic lymph nodes in the central neck compartment, presence of distant metastases and younger age of patients at surgery. Patients who received extensive surgery had better relapse-free survival rates ($p < 0.001$).

Conclusion: Total thyroidectomy and bilateral central as well as lateral neck dissections for children and adolescents with papillary thyroid carcinoma was associated with substantial postoperative complications. Nevertheless, it is associated with better prognosis for young patients with thyroid cancer. Prophylactic compartment-oriented lymph node dissections to these patients could be the management protocol in experienced hands.

1. Introduction

Papillary thyroid carcinoma is a major challenge for paediatric endocrine surgeons in Belarus after the Chernobyl accident on 26th April 1986 followed by the subsequent radioiodine fallout. Since then, many children and adolescents developed radiation induced thyroid carcinoma. During the period (1988–2010), hundreds of patients, aged ≤18 years with papillary thyroid carcinoma have undergone surgical treatment in a single hospital (Republican Centre for Thyroid Tumours, Minsk, Belarus). However, the unique clinicopathological features of these patients, the treatment results and outcomes in this cohort remained to be recognised [1].

The optimal surgical management for children and adolescents with papillary carcinoma is unclear. The behaviour of papillary thyroid carcinoma in this group of patients greatly varied. Nevertheless, the current American Thyroid Association (ATA) Guidelines recommended total thyroidectomy for most children with thyroid carcinoma. Besides, in patients with pre-operative clinical or radiological evidence of neck metastasis, therapeutic lymph node

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dissection is recommended [1].

Previous experience in Belarus supported the implementation of total thyroidectomy with routine simultaneous central (Level VI) and bilateral (Levels II-IV) neck lymph node dissections as the initial surgery in children and adolescents with radiation induced papillary thyroid carcinoma based on the high incidence of nodal and distant metastases at presentation [2,3]. In addition, increased number of metastatic lymph nodes in the central neck compartment was associated with an increased risk to develop lateral as well as bilateral nodal disease [4].

The rational of performing lymph node dissection in patients having papillary thyroid carcinoma is to stage the initial disease extent, to facilitate the subsequent I^{131} therapy, and to improve the survival rates of patients with the cancer. However, the need of I^{131} therapy as well as the effect on subsequent outcome is uncertain for lymph node metastases discovered only at pathological examination. In adult with papillary thyroid carcinoma, majority of surgeons adopted “watch and wait” protocol [5]. This is largely due to the concern of the morbidity due to central or lateral neck dissections whereas the rate of progression from occult to overt disease is relatively low and uncommon. In addition, the patient could undergo reoperation for recurrent disease with curative intent as many papillary thyroid carcinomas have indolent behaviour [6].

In the current study, we aimed to analyse the prevalence of permanent adverse effects for adopting this specific surgical strategy for children and adolescents with solitary papillary thyroid carcinoma and their potential risk factors.

2. Material and methods

2.1. Study cohort and initial treatment

The Review Board of the Minsk Municipal Clinical hospital for Oncology in Minsk of Belarus approved the study. Informed consents were obtained at the time of surgery to share epidemiological, clinical, and morphological individual data for further investigations. The details of the patients’ presentations, family history of cancer, history of radiation exposure, surgical and pathological findings, use of adjunctive therapy and clinical outcomes were acquired from hospital charts and electronic medical records (in computerized database).

The subjects of this prospective study were children and adolescents who suffered from papillary thyroid carcinoma in the age range of 4–18 inclusive at surgery. Among them, patients with papillary thyroid carcinoma attributed to externally irradiation were labelled “external radiation-related” group (after therapeutic radiation for malignancies during childhood). In total, 25 patients surgically treated during the period 1995 to 2010 were identified to belong to this group. The second group was named “post-Chernobyl” and included 936 patients affected by internal radiation under various circumstances and to various amounts of I^{131} (the area-specific degree of radioactive I^{131} contamination exceeding 185 kBq/m^2) who were operated in the years 1990–2005 (post-Chernobyl period). The “sporadic” group comprised 208 patients with operation done for papillary thyroid carcinoma in the period of 1991–2010 who were born during the years 1987–1992 (from April 1, 1987 to December 31, 1992). There is no epidemiological evidence of radiation exposure in this group of patients. These patients were born long after the I^{131} full decomposition (April 26, 1986–July 28, 1986). There was no history of exposure to internal irradiation or therapeutic irradiation.

These patients with papillary thyroid carcinoma underwent resection of the thyroid (lobectomy, near total or total thyroidectomy) and lymph nodes (in the central and lateral compartments of the neck) according to the extent of disease at the time of diagnosis. In the early 1990s, surgeons in the Centre preferred thyroid lobectomy or subtotal thyroidectomy. Neck lymph node dissection was performed only in cases when preoperative ultrasound neck examination and biopsy revealed lymph node involvement. Since 1998, the strategy has switched to a more aggressive approach. Total thyroidectomy with central and bilateral neck lymph node dissection became more frequent, whereas conservative surgery was done only in cases of very small solitary intrathyroidal nodules with no evidence of metastases. All the lymph nodes were examined for the presence of papillary thyroid carcinoma. In addition, patients with residual/persistent thyroid cancer or distant metastases were treated with post-operative I^{131} ablation (radioactive iodine therapy given 4–6 weeks after surgery). This was followed by thyroid stimulating hormone-suppressive doses of levothyroxine with a mean dose of 2.0–2.5 g/kg body weight.

Patients with multi-focal thyroid carcinomas, diffuse sclerosing variant of papillary thyroid carcinoma, isthmus-localized carcinomas as well as having only central (Level VI) or only with ipsilateral (Levels II, III, IV) lymph node dissections were excluded from this study.

Plasma calcium level was tested twice in first post-operative day and once in second post-operative day in all patients. In patients with hypocalcaemia, plasma calcium was tested daily, until it returns to normal range. Hypoparathyroidism was defined as a concentration of parathyroid hormone under 10 ng/L (normal range 10–65 ng/L) correlated to hypocalcaemia of an ionized calcium level under 1.0 mmol/L (normal range is 1.12–1.32 mmol/L). In severe hypocalcaemia (ionized calcium under 0.94 mmol/L or muscular spasm and tetany), treatment included intravenous calcium gluconate and oral calcitriol (Rocaltrol) 1.5 mcg per day (0.5 mcg every 8 h) and oral calcium (Calcium-Sandoz Forte) 3 g per day (1 g every 8 h) plus calcitriol for asymptomatic patients. Permanent hypocalcaemia was defined as ionized calcium under 1.12 mmol/L at 6 months after surgery.

Vocal cord function was clinically evaluated during the first 24 h after surgery in patients who had hoarseness of voice, a change in voice, or extensive disease invading major structures in the neck. If there were no complaints from patients or preoperative evaluation did not reveal any impairments of vocal cord function, direct or indirect laryngoscopy was performed in all the patients to assess laryngeal nerve function in the first 24–48 h and in 3 months, 6 months and 12 months after surgical treatment. Inferior laryngeal nerves were identified and preserved in total thyroidectomy with dissection of central compartment lymph nodes (Level VI). We classified the injury as transient if the laryngeal nerve function recovered within 12 months after surgery. Otherwise, the injury was considered permanent. Neurological lesions (permanent if persistent 12 months after surgery) were registered with their specific clinical signs.

After surgery, all the children and adolescent patients with papillary thyroid carcinoma were seen in the outpatient clinic every three months for at least one year to assess L-thyroxine dosage and to evaluate eventual complications.

2.2. Follow-up

The follow up of the patients were from 7 to 28 years (median, 19.6 years). The data were from local and regional address bureaus, department of public health and forensic medical establishments (for patients who have suicided). Follow-up information consisted of clinical examination, thyroid function tests, and serum thyroglobulin and anti-thyroglobulin antibodies. Neck ultrasound scan, chest radiograph, diagnostic whole-body scans with ^{131}I (2–5 mCi) and serum thyroglobulin assay (off thyroid hormone therapy) were performed every 6–12 months during the first 2 years after surgery

and every 12 months after the first 2 years of observation.

Complete remission is defined as negative diagnostic results on whole-body scans and undetectable or low serum thyroglobulin level [˂2 ng/mL] tested with thyroid stimulating hormone stimulation, in the absence of anatomically definable disease on neck ultrasound scanning or chest computerized tomography. In the patients in complete remission, repeated evaluation was performed every 2 years for 4 years and every 5 years thereafter. Continual I^{131} courses were given to patients with evidence of local recurrence or distant metastases.

2.3. Pathological parameters

We used the eight editions of TNM classification for staging of the papillary thyroid carcinoma [7]. The dimensions of the thyroid gland as well as the carcinoma were based on direct measurements of the surgical thyroid specimens during macroscopic examination. Morphological features examined included: histological pattern, extra-thyroidal extension to peri-thyroidal tissue, abundant psammoma bodies, growth pattern (as well circumscribed or infiltrative tumour growth), lymphatic invasion, vascular invasion, desmoplastic stromal reaction and extranodal extension. Micro-metastases in neck lymph node were defined as the presence of metastatic deposits $\leq$2 mm in maximum dimension, whereas macro-metastases were defined as deposits >2 mm in maximal dimension.

2.4. Statistical analysis

Baseline characteristics were presented as counts and percentages in groups and compared using Fisher test for categorical variables; the countable variables were presented as median, lower and upper quartiles and compared using Mann-Whitney-Wilcoxon test.

Survival analysis was performed for relapse-free survival based on log-rank Mantel- Haenszel test. Multivariate logistic regression was used to define sets of important demographical, clinical and morphological characteristics associated with the permanent morbidity. At first, we included in analysis the variables that were statistically significant in univariate analysis; then backward elimination was applied to the preliminary logistic models based on Bayesian information criterion to prevent over-fitting. Once the most appropriate model was determined, the estimates of the respective parameters and their 95% confidence intervals (CIs) were calculated. Odds ratios (ORs) for variables (and their 95% CIs) were calculated using an exponential transformation of the respective parameters. *P*-value <0.05 was considered statistically significant for final inferences. We used the statistical software R, version 3.4.2 (R Project for Statistical Computing, http://www.r-project.org).

3. Results

Table 1 showed the frequencies of complications in children and adolescents with papillary thyroid carcinoma treated with an extended surgical approach versus less radical approach (Table 1). All children and adolescents surgically treated for papillary thyroid carcinoma (n = 1169) were distributed according to their morbidity status: 911 (77.9%) of them had no post-surgical complications, 133 (11.4%) patients had permanent and 125 (10.7%) had transient injuries. The lowest rate of complications occurred in patients treated with incomplete thyroid surgeries (non-total thyroidectomy). On the other hand, the highest rate of complications was detected ($p < 0.001$) in patients treated with total thyroidectomy combined with neck lymph node dissections. Therefore, the extent of surgery in children and adolescents treated for papillary thyroid carcinoma significantly influenced on the frequency of complications.

Remarkably, morbidity in patients treated with total thyroidectomy and central and ipsilateral neck lymph node dissections (24.0% of permanent and 16.1% of transitory complications) was much higher than in patients treated with total thyroidectomy and central + bilateral neck lymph node dissections (10.3 and 11.3% correspondingly). It is likely that contra-lateral neck lymph nodes had no metastases and removed without difficulties for prophylactic considerations. The relapse-free survival curves showed patients who underwent extensive thyroid surgery (Fig. 1A, 15-years relapse-free survival was $97.5 \pm 0.5\%$ for patients treated with total thyroidectomy and $85.6 \pm 1.9\%$ for their counterparts, $p < 0.001$). Besides, an extended approach for lymph-node surgery significantly lowered the probability of relapses compared to a less radical treatment (Fig. 1B). Therefore, 15-years relapse-free survival was $98.2 \pm 0.5\%$ for patients treated with central and bilateral neck compartment dissection, $92.6 \pm 1.7\%$ for patients treated with only central lymphadenectomy, $92.6 \pm 2.2\%$ for patients who were not treated with lymph-node surgery and $89.7 \pm 2.4\%$ for patients treated with central and ipsilateral neck compartment dissection, $p < 0.001$).

Table 2 showed the subgroup analysis according to aetiology of papillary thyroid carcinoma. No complication occurred in 76% (709 of 936) of patients in post-Chernobyl group, in 84% (21 of 25) of patients in a post-therapeutic group and in 76% (158 of 208) of patients in sporadic group. Therefore, no differences occurred between these cohorts of patients with references to post-surgical complications.

Further, we analysed the extension of surgical resection in relation to the complications were in 509 children and adolescents with solitary (non-diffuse, non-isthmic) papillary thyroid carcinoma nodule treated by initial total thyroidectomy and routine compartment oriented bilateral central as well as (unilateral or bilateral) neck dissections. In these 509 patients, 55% (n = 280) were adolescents (15–18 years old) and 34.4% (n = 175) were parapubertal children (aged 11–14 years old) at presentation. In this cohort of patients, they presented at advanced clinical stage (Table 3). Though 185 of 509 patients (36.3%) presented with unilateral small carcinoma (sized 1–10 mm), only 11.4% (n = 58) of all patients had no lymph node metastases (pN0). Ipsilateral nodal disease was diagnosed in 60.1% (n = 306) whereas bilateral lymph node metastases were noted in 10.6% (n = 54). Extra-nodal metastatic growth occurred in 168 (33.0%) patients with pN1a and in 114 (22.3%) children and adolescents with pN1b. In addition, minimal extra-thyroidal extension was diagnosed in 52.1% (n = 265) and 14.1% (n = 72) of patients had distant metastases at presentation.

In most patients (165 of 509; 32.4%), the carcinoma showed a mixture of papillary and follicular structures. Solid component was revealed in these tumours regularly (180 of 509, 35.4%). Lymphatic permeation (n = 471; 92.5%) and abundant psammoma bodies (n = 327; 64.2%) were common. In addition, extensive desmoplastic reaction (n = 194; 38.1%) and vascular invasion (n = 110; 21.6%) were noted in these patients.

After surgical treatment, there were 141 patients developing 154 complications (including 13 patients with 2 complications) specific to thyroid surgery. There were 77 transient and 77 permanent complications respectively. In the transient complications, there are 61 with hypoparathyroidism (61/77; 79%), 9 with recurrent laryngeal nerve palsy (7 unilateral and 2 bilateral, 9/77; 12%), 4 with lymphatic leakage (34/77; 5%) and 3 wound healing (3/77; 4%). For permanent surgical morbidity, there were hypoparathyroidism (n = 51/77; 66%), recurrent laryngeal nerve palsy (unilateral [n = 16] or bilateral [n = 8]) (n = 24/77; 31%) and glossopharyngeal nerve (n = 2/77; 3%) injury. These complications occurred in 70 of 509 patients (13.8%). Overall, there were 10% and 5% of these

Table 1
Frequencies of post-operative complications according to the extent of surgical treatment in children and adolescents with papillary thyroid carcinoma (percent in rows).

Initial surgical treatment, patients (n = 1169)	Complications, n (%)		
	no complications 911 (77.9)	permanent 133 (11.4)	transient 125 (10.7)
non-TT only, n = 137	132 (96.3)	3 (2.2)	2 (1.5)
non-TT + central neck LND (Level VI) n = 155	147 (94.8)	6 (3.9)	2 (1.3)
TT + central neck LND, n = 196	129 (65.8)	31 (15.8)	36 (18.4)
TT + central and lateral neck LND (levels VI + ipsilateral II-IV), n = 167	100 (59.9)	40 (24.0)	27 (16.1)
TT + central and bilateral neck LND, n = 514	403 (78.4)	53 (10.3)	58 (11.3)

TT-total thyroidectomy; LND-lymph node dissections.

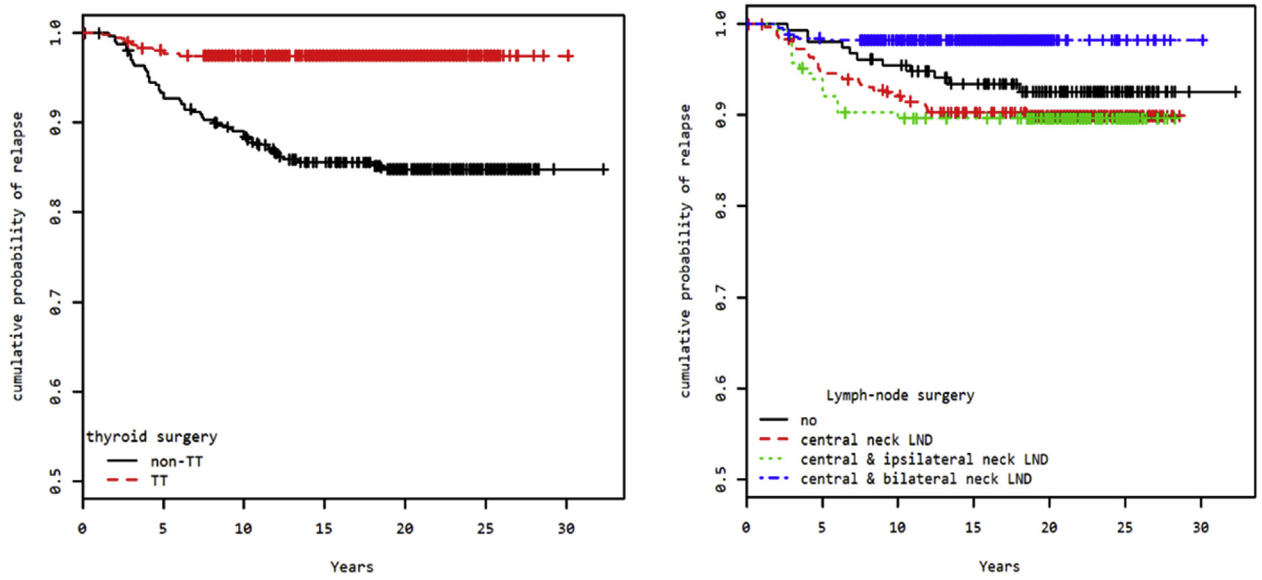

Fig. 1. Relapse-free survival curves of the whole cohort (n = 1169) by treatment: thyroid surgeries (left; 1A) and lymph-node surgeries (right; 1B).

Table 2
Surgical complications in children and adolescents treated for aetiologically different papillary thyroid carcinoma.

List of complications	Aetiology of papillary thyroid carcinoma			All patients
	post-Chernobyl	post-therapeutic	sporadic	
Postsurgical hypothyroidism (hypocalcaemia) transitory	81	2	22	105
Postsurgical hypothyroidism (hypocalcaemia) permanent	76	1	15	92
Recurrent laryngeal nerve (RLN) injury (vocal cord paresis or paralysis) Unilateral and transient	7	0	5	12
Recurrent laryngeal nerve (RLN) injury (vocal cord paresis or paralysis) Bilateral and transient	3	0	2	5
Recurrent laryngeal nerve (RLN) injury (vocal cord paresis or paralysis); Unilateral and permanent	38	0	3	41
Recurrent laryngeal nerve (RLN) injury (vocal cord paresis or paralysis) Bilateral and Permanent	9	0	1	10
Glossopharyngeal nerve injury (permanent)	6	0	0	6
Bleeding	2	0	3	5
Lymphorrhea	5	0	0	5

patients had permanent hypoparathyroidism and recurrent laryngeal nerve palsy respectively.

Of the 70 patients with post-surgical permanent complications, eight had no nodal metastasis (n = 4) or had only micro-metastases in the resected lymph nodes (n = 4). Permanent recurrent laryngeal nerve palsy occurred in 24 patients, including 16 unilateral and 8 bilateral injuries. Of these 24 patients, one had concurrent transitory hypoparathyroidism and 7 with simultaneous permanent hypoparathyroidism. Other combinations of concurrent morbidities included: transient hypoparathyroidism and transient unilateral recurrent laryngeal nerve palsy (1), permanent hypoparathyroidism and transient unilateral recurrent laryngeal nerve palsy (1), wound bleeding and transient hypoparathyroidism (1), glossopharyngeal nerve injury and transient hypoparathyroidism (1).

The recurrent laryngeal nerve palsy occurred in patients with advanced thyroid carcinomas directly invaded the trunk of the recurrent laryngeal nerve, after the release of the nerve from the carcinoma or because of traction injuries. Two patients with permanent recurrent laryngeal nerve injury had micro-metastases: one had papillary thyroid microcarcinoma with lymph node

Table 3
Children and adolescents with papillary thyroid carcinoma treated with total thyroidectomy and simultaneous central and bilateral lymph node surgery: comparison of factors associated with permanent surgical morbidity.

Clinical and morphological characteristics	Permanent surgical morbidity N = 70 (13.8%)	No permanent surgical morbidity N = 439 (86.2%)	*p*-value
Demographical/clinical data			
Age at operation n (%)			**<0.001**
4-10	15 (21.4)	39 (8.9)	
11-14	33 (47.1)	142 (32.3)	
15-18	22 (31.4)	258 (58.8)	
Sex			0.140
male	29 (41.4)	139 (31.7)	
female	41 (58.6)	300 (68.3)	
Male to female ratio	1:1.4	1:2.2	
Aetiology			0.130
Sporadic	13 (18.6)	123 (28)	
Post-radiation (Chernobyl)	57 (81.4)	316 (72)	
Tumour size, mm n (%)			**<0.001**
1-10	17 (24.3)	168 (38.3)	
11-20	34 (48.6)	219 (49.9)	
≥21	19 (27.1)	52 (11.8)	
Maximal size of metastatic lymph node, median (Q25; Q75, any level)	20 (15; 29)	15 (10; 20)	**<0.001**
Nodal disease, n (%)			**<0.001**
N0	4 (5.7)	54 (12.3)	
N1a	6 (8.6)	85 (19.4)	
N1b ipsilateral	44 (62.9)	262 (59.7)	
N1b bilateral	16 (22.9)	38 (8.7)	
Distant metastases	28 (40)	44 (10)	**<0.001**
Surgery for the neck lymph nodes			
Number of lymph nodes removed in the central compartment lymph node dissections, median (Q25; Q75)	9 (6; 13)	8 (5; 12)	**0.038**
Number of metastatic lymph nodes removed in the central neck compartment lymph node dissections (Level VI), median (Q25; Q75)	6 (4; 9)	3 (1; 5)	**<0.001**
Number of metastatic lymph nodes removed in the ipsilateral neck compartment lymph node dissections (Level II-IV), median (Q25; Q75)	2 (1; 4)	1 (0; 3)	**<0.001**
Patients with metastatic lymph nodes removed in the central neck compartment lymph node dissection (Level VI), n (%)	64 (91.4)	356 (81.1)	**0.041**
Patients with metastatic lymph nodes removed in the ipsilateral neck compartment lymph node dissection (Level II-IV), n (%)	60 (85.7)	300 (68.3)	**0.005**
Patients with metastatic lymph node removed in the contralateral neck compartment lymph node dissection (Level II-IV), n (%)	16 (40)	38 (10.9)	**<0.001**
The extent of lymph node involvement (any level)			**<0.001**
N0+N1 micro-metastases only	8 (11.4)	161 (36.7)	
Macroscopic metastases (clinically apparent), micro-metastases and macroscopic metastases	12 (17.1)	134 (30.5)	
Metastasis in lymph node(s) fixed to one another (matted) or to other structures (with extranodal extension)	50 (71.4)	144 (32.8)	
Pathology data			
Minimal extra-thyroidal extension in adipose tissue/perineural space n (%)	46 (65.7)	219 (49.9)	**0.020**
Minimal extra-thyroidal extension in muscle tissue or the trachea (pT3b/T4a in the 8ed of TNM classification), n (%)	10 (14.3)	24 (5.5)	**0.013**
Histological patterns, n (%)			**<0.001**
Pure papillary	3 (4.3)	91 (20.7)	
Pure follicular	8 (11.4)	62 (14.1)	
Papillary and follicular	20 (28.6)	145 (33)	
Solid areas present	39 (55.7)	141 (32.1)	
Extensive desmoplastic reaction n (%)	29 (41.4)	165 (37.6)	0.630
Vascular invasion, n (%)	26 (37.1)	84 (19.1)	**<0.001**
Lymphatic invasion, n (%)	68 (97.1)	403 (91.8)	0.182
Extensive psammoma bodies dissemination, n (%)	45 (64.3)	282 (64.2)	>0.99
Extensive lymphocytes infiltration, n (%)	11 (15.7)	72 (16.4)	>0.99
Comorbidity, n (%)			0.757
No	56 (80)	362 (82.5)	
autoimmune thyroiditis	10 (14.3)	60 (13.7)	
nodular hyperplasia/follicular adenoma	(5.7)	17 (3.9)	

involvement (pN1a) and one had minimal extra-thyroidal extension into adipose tissue and lymph nodal disease (pN1b).

One of the eight patients with bilateral recurrent laryngeal nerve palsy died of additional complications. In the other patients, five had recovery of bilateral function after two years of rehabilitation and one had unilateral recovery. One patient had permanent bilateral cord palsy.

Table 3 showed the risk factors associated with permanent surgical morbidity in this group of patients. Younger age at presentation (children of 4 to14-years-old versus adolescents 15 to18-years-old), larger tumour size (nodules sized 1–10 mm versus nodules sized ≥11 mm), widespread nodal disease (N1a vs N1b bilateral) and the presence of distant metastases were associated with significantly higher surgical morbidity ($p < 0.001$). The gender and the radiation as aetiology of cancer do not affect the post-operative morbidity of the patients.

The bilateral removal of clinically apparent or/and uninvolved lymph nodes in the central neck compartment (level VI) yielded (in median, Q25; Q75) nine (6; 13) lymph nodes in patients with permanent surgical morbidity and eight (5; 12) lymph nodes in

patients without such complications ($p = 0.038$). The number of metastatic lymph nodules removed in the central neck compartment lymph node dissections (median, Q25; Q75) was six (4; 9) in patients with permanent surgical morbidity and three (1; 5) in patients without such complications ($p < 0.001$). Similar correlations were also obtained in analysing the neck lymph nodes in the lateral compartment. In addition, the larger the size of metastatic lymph nodes and presence of extra-nodal growth at any level were strongly associated with occurrence of surgical complications in patients. In analysing the pathological risk factors (Table 3), the presence of minimal extra-thyroidal extension, solid growth pattern and vascular invasion were associated with permanent surgical morbidity ($p < 0.05$).

In multi-factorial analysis (Table 4), four clinicopathological factors showed significant associations with surgical morbidity. These include pN1 with extra-nodal extension (OR = 2.5, 95%CI 1.3–4.8), > four lymph nodes involved (OR = 2.5, 95%CI 1.4–4.5) in the central neck compartment, the presence of distant metastases (OR = 2.9, 95%CI 1.5–5.4) and young age of patients at presentation (OR = 2.1, 95%CI 1.2–3.8).

The hypothesis that unintentional removal of the parathyroid gland (s) could lead to the transient or permanent hypoparathyroidism was analysed. The parathyroid gland (s) were detected in 19% (97 of 509) surgically removed tissues and hypoparathyroidism occurred in 26% (25 of 97). Very occasionally, papillary thyroid carcinoma could invade the parathyroid gland (Fig. 2). On the other hand, hypoparathyroidism occurred in 21% (87 of 412) of patients without parathyroid detected in resected specimens. Therefore, there is no statistical correlation between the histological detection of parathyroid gland (s) in thyroidectomy and hypoparathyroidism.

Permanent hypoparathyroidism was noted in three patients with small (T1a), papillary thyroid carcinoma with no lymph node metastasis as well as in one patient with pT1b tumour and nodal micro-metastases in central compartment of neck dissection. There were also two patients with permanent hypoparathyroidism where carcinoma invaded the adipose tissue beyond the thyroid gland (one without nodal disease and the other one with micro-metastases pN1b).

None of the patient died of papillary thyroid carcinoma. Of the 509 patients, only one patient died of the surgical complication. Overall, the presence of complications related to the lymph node dissection did not affect the survival of patients with papillary thyroid carcinoma.

4. Discussion

The morbidity associated with the central neck dissection in addition to the total thyroidectomy was debated in several papers. Giordano et al. reported that in patients (their age was not defined) with total thyroidectomy and bilateral central neck dissection for metastatic papillary thyroid carcinoma in the both lobes or in the isthmus of the thyroid gland, surgery was associated with a higher rate of transient and permanent hypoparathyroidism (51.9% and 16.2% correspondingly). In addition, the rate of transient and

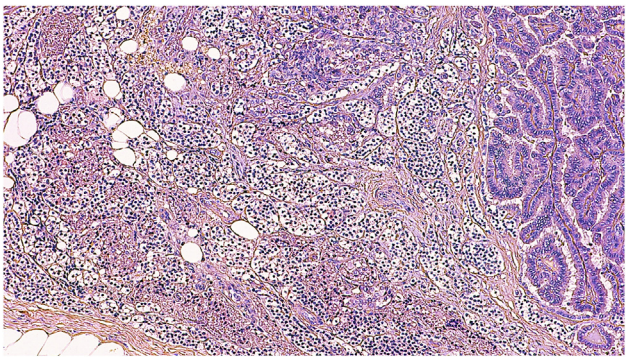

Fig. 2. Involvement of parathyroid gland by papillary thyroid carcinoma (haematoxylin and eosin x 100).

permanent recurrent laryngeal nerve injury was 5.5 and 2.3% respectively [8]. In patients of different age groups having total thyroidectomy and central neck dissection for various types of thyroid carcinomas (papillary, medullary and anaplastic carcinomas), 0.7% of patients had bilateral temporary laryngeal recurrent nerve palsy, 3.5% with unilateral temporary laryngeal recurrent nerve palsy, 1.6% with unilateral permanent laryngeal recurrent nerve palsy, 17.6% with temporary hypoparathyroidism and 4.4% with permanent hypoparathyroidism [9]. After lateral neck dissection of lymph nodes in levels from II to V (modified radical neck dissection or radical neck dissection), there were a few cases of permanent neural dysfunction and some transient complications (haemorrhage, respiratory distress, salivary or chylous fistula, and nervous lesion) [9].

On the other hand, the other group reported much lower overall frequency of permanent morbidity in adult patients with biochemically verified or suspected medullary thyroid carcinoma, as well as patients with papillary thyroid carcinoma – the rate of permanent hypoparathyroidism and palsy of the recurrent laryngeal nerve was negligible (1%) [10]. Furthermore, in a Korean study on adult patients with papillary thyroid carcinoma having nodal disease, postoperative temporary and permanent hypocalcaemia occurred in 34.1% and 6.2% patients correspondingly after total thyroidectomy and neck dissection. Temporary or permanent vocal fold paralysis occurred only in patients who underwent the sacrifice of the unilateral vocal folds directly invaded by tumour [11].

In our study permanent surgical morbidity occurred in 13.8% of the patients treated with extensive surgical approach. Hypoparathyroidism accounts for approximately two third of the permanent complications and recurrent laryngeal nerve palsy accounted for the remaining one third of the permanent complications. Overall, approximately 10% of the patients had permanent hypoparathyroidism and 5% had recurrent laryngeal nerve palsy. Thus, the incidence of surgical morbidity falls in the range reported in the literature.

Transient or permanent hypoparathyroidism is the most common post-operative complication. It occurred in approximately one

Table 4
Independent factors associated with permanent surgical morbidity.

Variables	Regression co-efficient (β)	p-value	Odd Ratio (OR)	95% Confidence level (CI)
Age at operation (4–14 versus 15-18-year-old)	0.75	0.012	2.1	1.2–3.8
Extra-nodal metastatic growth (any number, any neck lymph node compartment)	0.93	0.004	2.5	1.3–4.8
Number of metastatic lymph nodes removed in the central neck compartment lymph node dissection (Level VI) >4	0.91	0.002	2.5	1.4–4.5
Distant metastases	1.06	0.001	2.9	1.5–5.5

fifth of the patients. The accidental removal of parathyroid glands in conjunction with the thyroid gland and/or central neck compartment with lymph nodes is not the main reason leading to the development of permanent postoperative hypoparathyroidism. Apparently, disturbance of blood supply during surgery, as well as haemorrhage and fibrotic processes in the postoperative period played more important role in our patients. Permanent hypoparathyroidism could also occur with direct involvement of the parathyroid gland by papillary thyroid carcinoma, but this is uncommon. For recurrent laryngeal palsy or glossopharyngeal nerve injury, the complication could be related to the complex anatomy of the in the region along the path of the nerve and the direct involvement by carcinoma.

A few studies have addressed the surgical morbidity in children and adolescents with papillary thyroid carcinoma. For instance, Spinelli and colleagues showed that all surgical complications occurred exclusively in connection to total thyroidectomy. In this group of patients (which included diffuse sclerosing variant of papillary thyroid carcinoma or with bilateral and multifocal nodules), the overall rate of surgical complications was 20.8% (transient and permanent hypoparathyroidism were 13.6% and 4.4% respectively). The vocal fold palsy was unilateral in 2% and bilateral in 0.8% [12]. Machens and co-workers discussed the experience on a group of children and adolescents with thyroid lesions treated with total thyroidectomy with or without central node dissection. In the study, only 26.1% (60 of 230) were papillary thyroid carcinoma and the others were follicular carcinoma, medullary carcinoma and C-cell hyperplasia. There are no data on the exact number of papillary thyroid carcinoma with post-surgical complications. Nevertheless, transient recurrent laryngeal nerve palsy occurred in 3.5%, whereas transient and permanent hypoparathyroidism in 23.9% and 5.7% of all patients correspondingly [13]. According to the results of the study, transient recurrent laryngeal nerve palsy was associated only with central node dissection, whereas transient and permanent hypoparathyroidism were linked to patient age, central node dissection and the number of nodes cleared on central node dissection [12]. Based on the results, authors argued against the prophylactic ("elective") central neck lymph node dissection for clinically node-negative (cN0) papillary thyroid cancer.

In children and adults with papillary thyroid carcinoma, the overall permanent morbidity of thyroidectomy and lymph node dissection was comparatively low. However, there are different ways to interpret the data. Some advocates compartmental neck dissections and ready to recommend extended lymph node surgery (prophylactically) [10]. On the other hand, others do not recognize the benefit to the patients with respect to having correct staging and improving efficiency of I^{131} treatment [13].

In this study, we noted that the extent of surgery in children and adolescents treated for papillary thyroid carcinoma significantly influenced on the frequency of complications. In addition, morbidity in patients treated with total thyroidectomy and central plus ipsilateral neck lymph node dissections was much higher than in patients treated with total thyroidectomy and central plus bilateral neck lymph node dissections. Bilateral neck lymph node dissections performed by experienced hands do not add to morbidity that is largely depends on total thyroidectomy and dissection of the central lymph-node compartment of the neck.

In the present study, the relapse-free survival for the patients who had extensive thyroid surgery had better relapse-free survival. Thus, in children and adolescents, total thyroidectomy with bilateral neck lymph node dissection and bilateral central neck lymph node dissection was the most efficient procedure that permitted accurate staging and guided of subsequent management and follow-up.

Our study is not aiming to reconcile hostile camps or to offer a different way in the management of children and adolescents with papillary thyroid carcinoma. We presented a unique cohort of patients where long known factors that play a negative role in the spread of the tumour and increase the risk of its recurrence. Thus, we have excluded many patients from the study: in whom the tumour extended diffusely in the lobe (s) of the thyroid gland (diffuse sclerosing variant), tumours with multifocal unilateral and bilateral nodules, and carcinomas with localization in the isthmus and/or pyramidal lobe.

In the present study, patients with radiogenic (post-Chernobyl) and sporadic papillary thyroid carcinoma formed a rather monomorphic (age, localization, histology, surgical treatment received) group. This contrasts with the previous work of Demidchik and colleagues which investigated only children ($\leq$14 years of age at presentation) with papillary and medullary thyroid carcinoma as well, with an exceptional variety of primary surgeries [14]. In our opinion, the initially "aggressive" surgical tactic indeed explains the fact that the survival in these two aetiologically different groups of patients does not differ, even though post-Chernobyl papillary thyroid carcinoma is characterized by more advanced stage at presentation. Moreover, as shown in our previous studies, cancer relapses occurred in only 2.75% (14 of 509) of patients with papillary thyroid carcinoma [4]. Of these 14 patients, ten had distant metastases diagnosed according to the results of whole-body scans and four had regional recurrences that were confirmed by pathology. All these children and adolescents with relapses of papillary thyroid carcinoma presented had pN1b nodal disease. The 10-years relapse-free survival in this research was 97.2% (95% CI, 95.8–98.7).

Our study provides insights into the characteristics of surgical treatment and associated morbidity of children and adolescents with papillary thyroid carcinoma. The predominant prognostic issue with nodal metastasis is in increased risk of subsequent nodal recurrence. Therefore, lymph node surgery at presentation of children and adolescents with papillary thyroid carcinoma is the most efficient treatment modality or permits an accurate staging of the initial carcinoma extent at least. The results of this investigation showed that the lateral or bilateral neck dissections in children and adolescents in the high-volume centre did not add to permanent surgical complications. Surgical morbidity was related to the young age of the patient as well as extensiveness of the carcinoma (extranodal lymph node invasion, number of lymph nodes involved and distant metastases). There is no significant difference in survival between patient with or without surgical complications. Thus, we recommend radical surgery in paediatric population exclusively in specialized high-volume hospitals with unique clinical and morphological experience. Though the current approach is more aggressive compared with the usual practice in the Western countries, our local experience of a large, high-risk paediatric cohort of radiation-induced papillary thyroid carcinoma leads us to employ initially treatment (total thyroidectomy with bilateral and central compartment-oriented neck dissections) as well as subsequent repeated iodine-131 administration to make final outcomes of the patients more favourable.

Conflict of interest

None.

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